REMARKS

Claim Amendments

Claims 15-16, 38-40, 49 and 53-57 have been cancelled, without prejudice to or disclaimer of the subject matter therein.

Support for the amendment to Claim 1 is found in the specification on page 18, lines 5-10, and page 21, lines 12-14.

Support for the amendment to "at least 600 amino acids" in Claim 14 is supported in the specification on page 38, lines 10-11.

New Claims 58-60 simply draw out particular embodiments of Claims 1 and 14.

All other amendments are clerical in nature.

Rejection of Claims 1-5, 7, 8, 15, 16, 38-40, 46-48 and 53-59 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 1-5, 7, 8, 15, 16, 38-40, 46-48 and 53-59 under 35 U.S.C. §112, second paragraph, contending that these claims are indefinite due to the use of the term "consisting essentially of". The Examiner asserts that it is unclear how peptides that differ by one substitution of SEQ ID NO:2 or SEQ ID NO:4 as claimed in Claim 1(d), Claim 4 and Claim 5. The Examiner further contends that it is unclear as to what is encompassed by a fragment that is consisting essentially of a SEQ ID NO.

The rejection under 35 U.S.C. § 112, second paragraph is respectfully traversed. First, with respect to Claims 1(d), 4 and 5, these claims have been amended to clarify the claims and address the Examiner's concern.

With respect to the question of what is encompassed by a fragment that is consisting essentially of a SEQ ID NO, it is respectfully asserted that none of the claims recite a fragment that consists essentially of a SEQ ID NO. Claim 1(b) simply recites a biologically active fragment of SEQ ID NO:2. Accordingly, this claim is believed to be clear.

In view of the foregoing discussion, withdrawal of the rejection of Claims 1-5, 7, 8, 15, 16, 38-40, 46-48 and 53-59 under 35 U.S.C. §112, second paragraph is respectfully requested.

Objection to the Specification and Rejection of Claims 1-8, 14-16, 38-40, 46-52 and 55-57 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1-8, 14-16, 38-40, 46-52 and 55-57 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, the Examiner contends that the specification is enabling for a composition comprising SEQ ID NO:4 or peptides with the singular modification that affects the formation of normal nuclear lamina structures, and the differentiation of skeletal and cardiac myoblasts, but the Examiner asserts that the specification is not enabling for isolated complexes comprising

fragments, peptides that differ by at least one substitution, deletion, or insertion, or peptides that are at least 70% identical to SEQ ID NO:2 or SEQ ID NO:4.

Applicants traverse the rejection of Claims 1-8, 14-16, 38-40, 46-52 and 55-57 under 35 U.S.C. § 112, first paragraph. The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Further, it is a tenet of patent law that an applicant need not teach what the skilled artisan already knows. Instead, it is preferred that an applicant "omit what is known in the art." *Hybritech Inc. v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

First, with regard to the arguments submitted in the response filed February 15, 2006, the Examiner notes that the references of Xie et al. and Sherrill et al. were not included with the response. These references are included here, and the prior arguments relevant to these references are again asserted by reference to the February 15 response.

Second, the Examiner contends that the specification does not describe the biological activity of peptides that consist essentially of SEQ ID NO:2, peptides that are 70% identical to SEQ ID NO:2 and peptides that differ from SEQ ID NO:2 by one substitution, deletion or insertion of an amino acid.

In reply, Applicants submit that, contrary to the Examiner's assertion, the specification describes the biological activity of SEQ ID NO:2, as well as peptides that consist essentially of such peptide and the claimed variants thereof. Specifically, the specification teaches on page 12, lines 5-9, that the prelamin A prepeptide sequence (which includes the human version of the peptide represented by SEQ ID NO:2, as well as variants and prelamin A prepeptides from other species of animals) functions as a signaling molecule when proteolytically released from the prelamin A protein, indicating the proximity and direction of mononucleate myoblasts during differentiation and cell fusion to generate multinucleate myocytes. On page 13, lines 21-24, the specification teaches that the prelamin A prepeptide functions in the intercellular signaling between mononucleated myoblasts during cell fusion and the formation of multinucleated myocytes. On page 18, lines 6-14, the specification teaches the use of the prelamin A prepeptide for the promotion of myoblast activation and differentiation. On page 21, lines 12-20, the specification teaches that the prelamin A prepeptide promotes cell fusion and regeneration of

cardiac and skeletal myocytes, and promotes myocyte differentiation and myocyte organization. Accordingly, the specification is clear that the prelamin A prepeptide is a signaling molecule that promotes myoblast differentiation. These teachings are supported by the Examples in the specification. Given the guidance provided in the specification, one of skill in the art would readily be able to determine whether the claimed homologues of SEQ ID NO:2 have the required activity. The specification provides assays (see Examples) that one can use to confirm the activity, which contradicts the Examiner's assertion that the specification does not provide guidance to determine which fragments and homologues might work.

Applicants additionally submit herewith a Declaration under 37 CFR 1.132 of the inventor, Gary Brodsky, which provides additional supporting evidence that the prelamin A prepeptide, including the peptide represented by SEQ ID NO:2 and a peptide that is only about 53% identical to SEQ ID NO:2 (a chicken prelamin A prepeptide represented by SEQ ID NO:17), promotes myoblast fusion, myocyte activation, myocyte differentiation, and myocyte organization in myoblasts (see paragraphs 4 and 5). Notably, the myoblasts used in the experiments described in the Declaration were from *mouse*, and the prelamin A prepeptides were synthesized based on the human and chicken prelamin A prepeptide sequences, illustrating the ability of the peptide represented by Claim 1 to work across species.

As noted in the Declaration, the chicken prelamin A prepeptide contains a substitution, as compared to SEQ ID NO:2, at each of positions 1, 4, 5, 6, 9, 11 and 14, *as well as* two insertions between residues 12 and 13 with respect to SEQ ID NO:2. Accordingly, the experiment demonstrates that *multiple* substitutions and insertions can be made in SEQ ID NO:2, all in accordance with what is taught in the specification on pages 35-37, while retaining the biological activity of the prelamin A prepeptide. Indeed, even a substitution at position 4, which is highly conserved among other animal species (see Fig. 2 of the application), retains the activity of SEQ ID NO:2. Since the claimed peptides having at least 70% identity to SEQ ID NO:2 or that have only one modification at positions 1, 2, 5, 6, 9, 10, 11, 12, 13 or 14 are more similar to SEQ ID NO:2 than the chicken prelamin A prepeptide represented by SEQ ID NO:1, it is asserted that these data clearly support Applicants' contention that one of skill in the art is enabled to make and use the invention as presently claimed.

Moreover, as previously asserted, given the guidance provided in the specification discussed above regarding likely positions of SEQ ID NO:2 for modification, the number of residues that one would delete to form a fragment would be limited, such that one of skill in the art could readily make and use functional fragments of SEQ ID NO:2 (*e.g.*, one would not truncate the protein at position 15, and only positions 1 and 2 are recommended for modification by the specification).

Third, the Examiner contends that the specification does not describe a composition that promotes myoblast activation and growth or regeneration of cardiac or skeletal muscle

comprising a fragment of SEQ ID NO:4 or an amino acid sequence that is at least 70% identical to SEQ ID NO:4.

Initially, it is noted that the claims now recite a more clearly defined fragment of SEQ ID NO:4 that is at least 600 amino acids in length and a protein that is at least *95%* identical to SEQ ID NO:4. Applicants submit that the present specification provides sufficient guidance regarding what residues of prelamin A (SEQ ID NO:4) are predicted to tolerate modification. Indeed, SEQ ID NO:4 comprises SEQ ID NO:2, and so any of the modifications described above with respect to SEQ ID NO:2 are applicable to SEQ ID NO:4. As shown above, even this highly active portion of the protein can tolerate significant modification without impacting function. Again, the specification, at page 34-37, provides a detailed discussion of conservation or variation of the amino acids across species, and further discusses the importance of position 661 of SEQ ID NO:4. The specification provides evidence that at least six different mutations in prelamin A are asserting their effect by negatively impacting prelamin A processing, thus providing information regarding residues that should be avoided in order to produce a functional prelamin A. Furthermore, at the time of the invention, the nucleic acid and amino acid sequences of prelamin A were known for a variety of animal species, including, but not limited to: human mouse, chicken, *Xenopus laevis* (African clawed frog), and *Danio rerio* (zebra fish). These are all provided by the present specification and are more divergent than the claimed 95% identity. Accordingly, one of skill in the art can readily determine which residues are likely to tolerate modification and make and use the claimed modified proteins without undue experimentation. The specification also demonstrates the role of prelamin A in myoblast differentiation (see Examples), which is further illustrated in the Declaration of Dr. Brodsky enclosed herewith (see paragraph 6). The guidance provided by the specification as further supported by the enclosed Declaration illustrate that one of skill in the art would find the presently claimed invention fully enabled.

In view of the foregoing remarks, the withdrawal of the rejection of Claims 1-8, 14-16, 38-40, 46-52 and 55-57 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Objection to the Specification and Rejection of Claims 1-5, 7-8, 14-16, 38, 39, 46, 47, 50, 51, 55, 56 and 57 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1-5, 7-8, 14-16, 38, 39, 46, 47, 50, 51, 55, 56 and 57 under 35 U.S.C. § 112, first paragraph, on the basis of written description. In reply to Applicants' response filed February 15, 2006, the Examiner contends that the specification does not describe the biological activity of SEQ ID NO:2, peptides that are 70% identical to SEQ ID NO:2 and peptides that differ from SEQ ID NO:2 by one substitution, deletion or insertion of an amino acid residue. The Examiner also asserts that the specification

does not describe prelamin A peptides with any amino acid substitutions other than those listed in Claim 40, or the fragments of SEQ ID NO:4 with internuclear transport domain activity.

Applicants traverse the rejection of Claims 1-5, 7-8, 14-16, 38, 39, 46, 47, 50, 51, 55, 56 and 57 under 35 U.S.C. § 112, first paragraph. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998).

Initially, Applicants refer to the discussion above, and submit that contrary to the Examiner's contention, the specification provides detailed guidance regarding which amino acids in the polypeptides can be altered without affecting the function of the specific polypeptide. Also, Claim 14 has been amended to claim variants with 95% identity and prelamin A activity, and fragments that are at least 600 amino acids in length with prelamin A activity. Claims 15-16 and 38-39, as well as dependent claims therefrom, have been cancelled, without prejudice to or disclaimer of the subject matter therein.

With regard to claims directed to SEQ ID NO:2, Applicants disagree with the Examiner's statement that the specification does not describe the biological activity of SEQ ID NO:2. To the contrary, as discussed above under the enablement rejection, the specification teaches that the prelamin A prepeptide sequence functions as a signaling molecule when proteolytically released from the prelamin A protein, indicating the proximity and direction of mononucleate myoblasts during differentiation and cell fusion to generate multinucleate myocytes, promoting myoblast activation and differentiation. The Examples in the specification and the additional evidence provided in the Declaration of Dr. Brodsky establish that SEQ ID NO:2 has such function. Further, as discussed in detail above, the present specification provides significant guidance at page 34, line 17 to page 37, line 2, with respect to which of *each* of the positions of the 15 amino acid sequence of SEQ ID NO:2 are candidates for modification and which are not. The accuracy of this description is *clearly* shown by the evidence provided in the attached Declaration that demonstrates that peptides with far greater variation than that claimed, including at the specific

positions identified by the inventor in the original specification, retain biological activity, as clearly predicted and stated by the inventor. The specification clearly discusses the impact of modification *at each position of SEQ ID NO:2* and clearly notes those residues that are important for function (*e.g.,* the cysteine residue at position 15 of SEQ ID NO:2). This is indeed a sufficient description to show possession of the invention and is corroborated by the specification and Declaration under 37 CFR § 1.132. Moreover, Applicants again assert that the number of variants encompassed by the claims is *not* large, noting that at 70% identity, only 4 or fewer amino acids can be modified. Indeed, the peptide described in the experiments in the Declaration is biologically active at only 53% identity to SEQ ID NO:2. With regard to deletion fragments, given the discussion with regard to which positions are likely to tolerate modification, it is clear that such fragments are limited, with deletions at positions 1 and 2 being the only likely candidates.

With regard to Claim 14, Applicants submit that one of skill in the art can also readily envision the proteins encompassed by these claims. The specification and the knowledge in the art at the time of the invention provide significant guidance regarding the processing site for prelamin A, as well as the residues of prelamin A that are rarely modified across species or vary (referring to discussions at page 18, line 17 to page 19, line 18; page 34, lines 17-25; and page 37, lines 10-19, for example). The specification has taught which residues are most important to the function of prelamin A by noting residues that are important with respect to the processing site and by identifying residues that, if modified, can render the prelamin A processing-deficient. The specification has provided an extremely detailed discussion of where the portion of SEQ ID NO:4 containing the signaling peptide of SEQ ID NO:2 can be modified, which is clearly demonstrated to be accurate by the supporting data provided with this response. One of skill in the art is readily able to envision proteins that are 95%, 97% or 99% identical to SEQ ID NO:4, and the specification provides assays that can be used to evaluate the function of the proteins.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-5, 7-8, 14-16, 38, 39, 46, 47, 50, 51, 55, 56 and 57 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 38 and 39 Under 35 U.S.C. §102(b):

The Examiner has rejected Claims 38 and 39 under 35 U.S.C. §102(b), contending that these claims are anticipated by Barton and Worman.

Claims 38 and 39 have been cancelled, without prejudice to or disclaimer of the subject matter therein. Accordingly, this rejection is moot, and the withdrawal of the rejection is respectfully requested.

Rejection of Claims 38, 39, 40 and 53-57 Under 35 U.S.C. §102(b)

The Examiner has rejected Claims 38, 39, 40 and 53-57 under 35 U.S.C. §102(b), contending that these claims are anticipated by Ostlund.

Claims 38, 39, 40 and 53-57 have been cancelled, without prejudice to or disclaimer of the subject matter therein. Accordingly, this rejection is moot, and the withdrawal of the rejection is respectfully requested.

Rejection of Claims 38, 39, 40 and 53-57 Under 35 U.S.C. §102(a) or 103

The Examiner has rejected Claims 38, 39, 40 and 53-57 under 35 U.S.C. §102(a), or in the alternative, § 103, contending that these claims are anticipated by or unpatentable over Favreau et al.

Claims 38, 39, 40 and 53-57 have been cancelled, without prejudice to or disclaimer of the subject matter therein. Accordingly, this rejection is moot, and the withdrawal of the rejection is respectfully requested.

Applicants have attempted to respond to all of the Examiner's concerns as set forth in the May 3, 2006 Office Action. Any questions or concerns regarding the claims or Applicants' position should be directed to the below-named agent at (303) 863-9700.

Respectfully submitted,

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